REQUEST FORM AND FORMALITIES PRELIMINARY AMENDMENT FOR FILING A PATENT APPLICATION UNDER 37 C.F.R. 1.53(b)
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THIS APPLICATION: DOCKET NUMBER	FILING DATE	PRIOR APPLICATION: EXAMINER	ART UNIT	TOTAL NO. OF PAGES
P62285US1	June 28, 2000	Berman, A.	1615	4

Address to:

Assistant Commissioner of Patents
Box Patent Application
Washington, D.C. 20231

This is a request for filing a [x] continuation or [ ] divisional application under 37 C.F.R. 1.53(b) of prior application Serial No. **09/125,810** filed on **August 26, 1998**, entitled **SLOW-RELEASE PHARMACEUTICAL FORMULATIONS CONTAINING MIZOLASTINE** by the following inventor(s).

	Family Name	First Given Name	Second Given Name
Full Name of Inventor	CHARIOT	Maryvonne	
	City	State or Foreign Country	Country of Citizenship
Residence & Citizenship	La Ville Du Bois	France	France
	Post Office Address	City	State & Zip Code/ Country
Post Office Address	22 ruelle des Néfliers	La Ville Du Bois	France 91620

	Family Name	First Given Name	Second Given Name
Full Name of Inventor	LEWIS	Gareth	
	City	State or Foreign Country	Country of Citizenship
Residence & Citizenship	Dourdan	France	Great Britain
	Post Office Address	City	State & Zip Code/ Country
Post Office Address	39 avenue de Paris	Dourdan	France 91410

	Family Name	First Given Name	Second Given Name
Full Name of Inventor	MONTEL	Jean	
	City	**State or Foreign Country**	**Country of Citizenship**
Residence & Citizenship	Chatou	France	France
	Post Office Address	**City**	**State & Zip Code/ Country**
Post Office Address	3 rue Le Val Sablon	Chatou	France 78400

[ ] additional sheet(s) with inventors information attached

1. [x] A Second Preliminary Amendment is enclosed.

2. [ ] Cancel claim(s) _____ for purposes of lessening filing fees.

The filing fee is calculated on the basis of the claims existing in the prior application as amended by 1 and/or 2 above.

			CLAIMS	
Basic Fee			$345	$690
Total Claims	23	- 20 = 3	x 9 = $	x 18 = $ 54
Ind. Claims	6	- 3 = 3	x 39 = $	x 78 = $234
[ ] Multiple Dependent Claims			+130 = $	+ 260 = $
			Total $	Total $978

3. [x] The Commissioner is hereby authorized to charge fees under 37 C.F.R. 1.16 and 1.17 which may be required or credit any overpayment to Deposit Account No. 06-1358. A duplicate copy of this sheet is enclosed.

4. [ ] This application is filed under Rule 53(f) and therefore the [ ] Filing Fee [ ] Declaration is not enclosed.

5. [x] A check in the amount of $978 is enclosed.

6. [x] Amend the specification by inserting before the first line the sentence:

--This is a continuation of application Serial No. 09/125,810, filed August 26, 1998, which is a 371 of PCT/FR97/00355, filed February 28, 1997. --

7. [ ] A verified statement claiming small entity status under 37 CFR 1.9 and 1.27:

a) [ ] was claimed by way of a declaration filed in prior application Serial No.

b) [ ] is claimed by way of the attached declaration.

8. [x] Priority of Application No. 96.02662 filed in France on March 4, 1996 is claimed under 35 U.S.C. 119.

a) [x] Certified copy of the priority document filed through the IB.

b) [ ] Certified copy filed herewith.

9. [x] The prior application is assigned of record to SYNTHELABO, Paris, France.

10. [x] The Power of Attorney in the prior application is to at least one of the following:

John Clarke Holman, 22,769; Harvey B. Jacobson, Jr., 20,85l; D. Douglas Price, 24,514; Marvin R. Stern, 20,640; Michael R. Slobasky, 26,421; Jonathan L. Scherer, 29,851; Irwin M. Aisenberg, 19,007; and William E. Player, 31,409.

a) [x] The power appears in the original papers of the prior application.

b) [ ] The New Power Of Attorney And Revocation Of Previous Powers, as well as the original power submitted subsequent to the filing of the application, are enclosed.

11. [x] Petition to extend the life of the above prior application to at least the date hereof

[ ] is being concurrently filed in that prior application.
[ ] was previously filed in that application.
[x] is not necessary.

If a Petition for Extension of Time is necessary and the Petition and/or the check is not enclosed, this will act as the Petition and applicant herewith petitions the Commissioner to extend the time for response and charge any fees necessary under 37 CFR 1.17 (a)(1)-(5) to Deposit Account No. 06-1358.

12. [ ] New formal drawings are enclosed.

13. [x] Enclosed is Form PTO-1449 listing prior art of record in parent application Serial No. 09/125,810, filed August 26,1998, which is relied on for an earlier filing date under 35 U.S.C. 120.

14. [ ] Also enclosed is:

Address all future correspondence to:

JACOBSON, PRICE, HOLMAN & STERN, PLLC
The Jenifer Building
400 Seventh Street, N.W.
Washington, D.C. 20004-2201
Telephone 202/638-6666
Customer No. 000136

Enclosed is a copy of the prior application, Serial No. 09/125,810, as originally filed on August 26, 1998.

Respectfully submitted,

By _____
Harvey B. Jacobson, Jr.
Reg. No. 20,851
JACOBSON, PRICE, HOLMAN & STERN, PLLC
400 Seventh Street, N.W.
Washington, D.C. 20004
(202) 638-6666

Dated: June 28, 2000

[x] Attorney or Agent of record

[ ] Filed under 37 CFR 1.34(a)

JCH-12/97-105

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Maryvonne CHARIOT et al

Serial No.

Filed:

Continuation Application of
Serial No. 09/125,810, filed
August 26, 1998

For: SLOW-RELEASE PHARMACEUTICAL
FORMULATIONS CONTAINING MIZOLASTINE

SECOND PRELIMINARY AMENDMENT

Asst. Commissioner of Patents
Washington, D.C. 20231

Sir:

Prior to initial examination, please amend the above-identified application as follows:

IN THE SPECIFICATION:

Page 1, last line, change "The Applicant Company has" to --Applicants have-- and change "its" to --their--.

Page 2, line 21, change "The Applicant Company has" to --Applicants have--;

after line 26, insert the following paragraphs:

-- Figure 1 shows the dissolution profile obtained with a formulation according to the invention;

Figure 2 shows the dissolution profile obtained with a formulation identical to that of the invention but containing no L-tartaric acid; and

Figure 3 shows the curves of the plasma kinetics of a pharmaceutical form according to the invention containing 10 mg of mizolastine studied in a healthy volunteer after a single oral administration, compared with a standard immediate-release gelatin capsule containing 10 mg of mizolastine.--

IN THE ABSTRACT:

Add the Abstract of the Disclosure appended hereto.

IN THE CLAIMS:

Claim 1, lines 2-3, change "characterized in that it contains" to --comprising--;

line 5, delete "with" and "said".

Claim 2, line 2, change "characterized in that" to --wherein--.

3. (Amended) Sustained-release pharmaceutical formulation according to [either of Claims 1 and 2] Claim 1, wherein [characterized in that] the fatty matrix is selected from the group consisting of [made with] hydrogenated castor oil, a [or with] hydrogenated lecithin, a [lecithin or] long-chain fatty acid and a triglyceride [acids or triglycerides] esterified with one, two or three medium-chain fatty acids.

4. (Amended) Sustained-release pharmaceutical formulation according to [any one of Claims 1 to 3] Claim 1, wherein [characterized in that] the organic acid is selected [chosen] from the group consisting of maleic, tartaric, malic, fumaric, lactic, citric, adipic and succinic acid [acids] in the form of a racemate [racemates] or an isomer [isomers].

Claim 5, line 2, change "any one of Claims 1 to 4" to --Claim 1--;

line 3, change "characterized in that" to --wherein--.

Claim 6, line 2, change "characterized in that" to --wherein--.

Claim 7, lines 1-2, change "any one of Claims 1 to 6" to --Claim 1--;

line 2, change "characterized in that" to --wherein the formulation--.

Add the following new claims:

--8. Coated sustained release tablet containing mizolastine, comprising a sustained-release tablet containing mizolastine, a fatty matrix and an organic acid, the coated tablet having a dissolution profile which is pH independent.

9. The tablet of claim 8, wherein the dissolution profile is one in which about 30 to 70% of the mizolastine is dissolved in 1 hour and 100% of the mizolastine is dissolved in 3 to 5 hours.

10. The tablet of Claim 8, wherein the weight ratio between the mizolastine and the organic acid is between 0.3 and 1.

11. The tablet of Claim 8, wherein the fatty matrix is selected from the group consisting of hydrogenated castor oil, a hydrogenated lecithin, a long-chain fatty acid and a triglyceride esterified with one, two or three medium-chain fatty acids.

12. The tablet of Claim 8, wherein the organic acid is selected from the group consisting of maleic, tartaric, malic, fumaric, lactic, citric, adipic and succinic acid in the form of a racemate or an isomer.

13. The tablet of Claim 8, wherein the organic acid is L-tartaric acid.

14. The tablet of Claim 13, wherein the ratio between the mizolastine and the L-tartaric acid is 0.5.

15. The tablet of Claim 8, wherein the formulation contains from 1 to 25 mg of mizolastine.

16. The tablet of Claim 8, wherein the organic acid has a pK of 2 or more.

17. Coated sustained-release tablet containing mizolastine, comprising a sustained-release tablet containing from 1 to 25 mg of mizolastine, a fatty matrix and an organic acid having a pK of 2 or more, the weight ratio between the mizolastine and the organic acid is between 0.3 and 1, the organic acid is L-tartaric acid.

18. The tablet of Claim 11, wherein the ratio between the mizolastine and the L-tartaric acid is 0.5

19. The tablet of Claim 18, wherein the fatty matrix is hydrogenated castor oil.

20. The tablet of Claim 19, wherein the tablet has a dissolution profile which is independent of pH and is one in which about 50% of the mizolastine is dissolved in 1 hour and 100% of the mizolastine is dissolved in 3 to 5 hours.

21. Coated sustained release tablet, consisting essentially of mizolastine, a fatty matrix, an organic acid and a coating.

22. Coated sustained release tablet, consisting essentially of mizolastine, a fatty matrix, an organic acid, and a coating, the coated tablet having a dissolution profile which is pH independent.

23. Coated sustained release tablet, consisting essentially of mizolastine, a fatty matrix, an organic acid, and a coating, the coated tablet having a dissolution profile which is pH independent, the organic acid being selected from the group consisting of maleic, tartaric, malic, fumaric, lactic, citric, adipic and succinic acid in the form of a racemate or an isomer.--

R E M A R K S

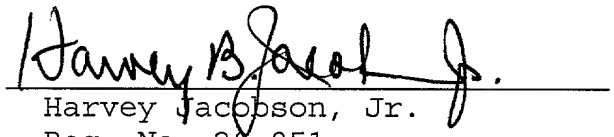
The present continuation is directed to cancelled claims 1-23 of the parent application.

In view of the foregoing, early action on the merits is respectfully requested.

Any fees required by the present Amendment may be charged to Deposit Account 06-1358.

Respectfully submitted,

JACOBSON, PRICE, HOLMAN & STERN, PLLC

By 

Harvey Jacobson, Jr.
Reg. No. 20,851

400 7th Street, N.W.
Washington, D.C. 20004
(202) 638-6666
Atty. Dkt. P62285US1

SUSTAINED-RELEASE PHARMACEUTICAL FORMULATIONS CONTAINING MIZOLASTINE

The present invention relates to novel sustained-release pharmaceutical formulations containing 2-[[1-[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]piperid-4-yl]methylamino]-pyrimidin-4-ol or 2-[[1-[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]piperid-4-yl]methylamino]-pyrimidine-4(1H)-one, or mizolastine, as active principle.

Mizolastine is described in European patent EP 0,217,700.

Mizolastine binds to the H_1 histamine receptor and inhibits the degranulation of mastocytes in vitro and in vivo. It can thus be used for the treatment of respiratory, cutaneous or ocular allergies and various allergic manifestations.

During the oral administration of immediate-release formulations containing mizolastine, undesirable sedative effects have been observed which are associated with the existence of a high peak in the plasma.

Consequently, it was necessary to find formulations for an oral administration which have a profile of release of the active principle such that it is possible to obtain a lower peak in the plasma without decreasing the bioavailability.

The Applicant Company has based its research

of such formulations on the study of the kinetics of dissolution of mizolastine. The reason for this is that mizolastine is a weak base (pK 5.6) which is sparingly soluble in water (13 mg/l at neutral pH) but much more soluble at acidic pH (11 g/l at pH 3); the first gelatin capsules released 100 % of mizolastine over 30 minutes in a dissolution medium at pH 2 whereas only 40 % were dissolved at pH 6.8.

Moreover, the release of mizolastine from the sustained-release pharmaceutical form according to the invention did not need to be influenced by the differences in pH in the gastrointestinal tract.

The aim of the present invention is to propose formulations containing mizolastine whose dissolution profile is as follows:

- about 30 to 70 % of mizolastine dissolved in 1 hour,
- 100 % of mizolastine dissolved in 3 to 5 hours, and
- pH-independent profile.

The Applicant Company has shown that tablets containing a core formed of a sustained-release tablet containing mizolastine combined with a fatty matrix and with an organic acid, the said tablet being coated to prevent degradation of the product by light, are entirely suitable.

The tablets according to the invention contain from 1 mg to 25 mg of mizolastine. These doses

correspond to concentrations of from 0.5 % to 12 % by weight of mizolastine.

The fatty matrix is made with hydrogenated castor oil or with hydrogenated lecithins or long-chain fatty acids, for example C_{12}-C_{28} long chain fatty acids such as behenic acid, or triglycerides esterified with medium-chain fatty acids, for example C_8-C_{18} fatty acids.

The organic acid preferably having a pK of 2 or more is chosen from maleic, tartaric, malic, fumaric, lactic, citric, adipic and succinic acids in the form of racemates or isomers. According to the invention, the acid particularly preferred is L-tartaric acid.

The weight ratio between the mizolastine and the organic acid should be between 0.3 and 1. With L-tartaric acid, this ratio is preferably equal to 0.5.

The tablets are prepared by granulation using the active principle, the agent constituting the fatty matrix, the organic acid and other excipients such as, for example, lactose, mannitol and sugars or similar sugar-alcohols, microcrystalline cellulose, starch, calcium phosphates and sulphates, polyvidone, and substituted celluloses such as hydroxypropyl-cellulose, hydroxypropylmethylcellulose or methylcellulose.

The granulation may be carried out in a wet phase, for example in the presence of water or alcohol, or may be performed by fusion or by compacting. The

granulation step may optionally be left out and the tablets prepared by direct tableting of the mixture of mizolastine and the excipients.

Anhydrous colloidal silica and magnesium stearate are added to the granules obtained and the mixture is tableted. The tablets are then covered with a coating film by spraying them with a coating solution in a machine with a fluidized-air bed or in a coating turbine.

The example which follows illustrates the invention without limiting it:

Tablet

	% (weight)
mizolastine	4.8
hydrogenated castor oil	12.0
lactose	60.0
microcrystalline cellulose	9.6
L-tartaric acid	9.6
polyvidone	2.9
anhydrous colloidal silica	0.2
magnesium stearate	0.9
purified water	Q.S.
Total	100.0

Coating

methylhydroxypropylcellulose	74.0
titanium dioxide (E171)	18.5

propylene glycol	7.5
purified water	Q.S.
Total	100.0

The dissolution profile obtained with a formulation according to the invention is given in Figure 1.

This profile gives about 50 % of product dissolved in 1 hour, 100 % of product dissolved in 3 to 5 hours, and it is independent of the pH.

The dissolution profile obtained with a formulation identical to that of the invention but containing no L-tartaric acid is given in Figure 2.

The plasma kinetics of a pharmaceutical form according to the invention containing 10 mg of mizolastine were studied in a healthy volunteer after a single oral administration, compared with a standard immediate-release gelatin capsule containing 10 mg of mizolastine.

Table 1 presents the kinetic parameters and Figure 3 the curves of the plasma kinetics, obtained respectively with each formulation; the plasma kinetics obtained with the pharmaceutical form according to the invention makes it possible to prevent any peak in the plasma without losing bioavailability.

The plasma kinetics of a pharmaceutical form according to the invention were also studied in comparison with the same formulation without L-tartaric

acid.

The study was performed on twelve healthy volunteers after a single oral administration of a tablet according to the invention containing 10 mg of mizolastine or the same tablet without L-tartaric acid.

Table 2 shows that the bioavailability of the formulation containing no L-tartaric acid represents only 43 % of that observed with the formulation according to the invention containing L-tartaric acid. The values of Cmax and the AUC values (0-∞) are respectively 1.5 and 2 times as high for the formulation containing L-tartaric acid as for that not containing any.

In addition, for the formulation with L-tartaric acid, the min.-max. variation indices are much lower, which suggests great uniformity in the release.

The results altogether show that the formulations according to the invention have:

- a pH-independent dissolution profile,
- an *in vivo* release which prevents any peak in the plasma,
- a bioavailability which is not decreased relative to an immediate-release formulation,
- lower variability of the plasma kinetics results.

CLAIMS

1. Sustained-release pharmaceutical formulation containing mizolastine, characterized in that it contains a core formed of a sustained-release tablet containing mizolastine combined with a fatty matrix and with an organic acid, the said tablet being coated.

2. Sustained-release pharmaceutical formulation according to Claim 1, characterized in that the weight ratio between the mizolastine and the organic acid is between 0.3 and 1.

3. Sustained-release pharmaceutical formulation according to either of Claims 1 and 2, characterized in that the fatty matrix is made with hydrogenated castor oil or with hydrogenated lecithins or long-chain fatty acids or triglycerides esterified with medium-chain fatty acids.

4. Sustained-release pharmaceutical formulation according to any one of Claims 1 to 3, characterized in that the organic acid is chosen from maleic, tartaric, malic, fumaric, lactic, citric, adipic and succinic acids in the form of racemates or isomers.

5. Sustained-release pharmaceutical formulation according to any one of Claims 1 to 4, characterized in that the organic acid is L-tartaric acid.

6. Sustained-release pharmaceutical formulation according to Claim 5, characterized in that the ratio between the mizolastine and the L-tartaric acid is 0.5.

7. Formulation according to any one of Claims 1 to 6, characterized in that it contains from 1 to 25 mg of mizolastine.

Abstract of the Disclosure

A sustained-release pharmaceutical formulation containing mizolastine, a core formed of a sustained-release table containing mizolastine combined with a fatty matrix and an organic acid, the tablet being coated.

DECLARATION AND POWER OF ATTORNEY U.S.A.

FOR ATTORNEYS' USE ONLY

ATTORNEYS' DOCKET NO. _____

ALL PATENTS, INCLUDING DESIGN
FOR APPLICATION BASED ON PCT, PARIS CONVENTION,
NON PRIORITY, OR PROVISIONAL APPLICATIONS

As a below named inventor, I declare that my residence, post office address and citizenship are stated below next to my name, the information given herein is true, that I believe that I am the original, first and sole inventor (if only one name is listed at 201 below), or a first and joint inventor (if plural inventors are named below at 201-203, or on additional sheets attached hereto) of the subject matter which is claimed and for which patent is sought on the invention entitled:

101 Slow-release pharmaceutical formulations containing mizolastin

102 which is described and claimed in: ☒ PCT International Application No. PCT/FR97/00355 filed February 28, 1997

☐ the attached specification ☐ the specification in application Serial No _____ filed _____

(if applicable) and amended on _____

I hereby state that I have reviewed and understand the contents of the above-identified specifications, including the claims, as amended by any amendment referred to above
I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.
I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s) (Number)	(Country)	(Day/Month/Year Filed)	Priority Claimed
9602662	FRANCE	March 4, 1996	☒ Yes ☐ No
103 _____	_____	_____	☐ Yes ☐ No
104 _____	_____	_____	☐ Yes ☐ No

I hereby claim the benefit under Title 35, United States Cod, §119(e) of any United States provisional appplication(s) listed below:
Application No. _____ Filing Date _____ Application No. _____ Filing Date _____

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

105 _____ (Application Serial No.) _____ (Filing Date) _____ (Status patented, pending, abandoned)

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorneys (Registration No.) to prosecute this application, receive and act on instructions from my agent, and transact all business in the Patent and Trademark Office connected therewith. HARVEY B. JACOBSON, JR. (20,851); D. DOUGLAS PRICE (24,514); JOHN CLARKE HOLMAN (22,769), MARVIN R. STERN (20,640); MICHAEL R. SLOBASKY (26,421); JONATHAN L. SCHERER (29, 851); STANFORD W. BERMAN (17,909); IRWIN M. AISENBERG (19,007); WILLIAM E. PLAYER (31,409)

SEND CORRESPONDENCE TO:	DIRECT TELEPHONE CALLS TO. (please use Attorney's Docket No.) (202) 638-6666
JACOBSON, PRICE, HOLMAN & STERN PROFESSIONAL LIMITED LIABILITY COMPANY 400 Seventh Street, N.W. Washington, D.C. 20004	JACOBSON, PRICE, HOLMAN & STERN PROFESSIONAL LIMITED LIABILITY COMPANY

*Inventor(s) name must include at least one unabbreviated first or middle name.

201	FULL NAME* OF INVENTOR	FAMILY NAME: CHARIOT	GIVEN NAME: Maryvonne	MIDDLE NAME:	
	RESIDENCE & CITIZENSHIP	CITY: La Ville Du Bois	STATE OR FOREIGN COUNTRY: France	COUNTRY OF CITIZENSHIP: french	
	POST OFFICE ADDRESS	POST OFFICE ADDRESS: 22 ruelle des Néfliers	CITY: La Ville Du Bois	STATE OR COUNTRY: France	ZIP CODE: 91620
202	FULL NAME* OF INVENTOR	FAMILY NAME: LEWIS	GIVEN NAME: Gareth	MIDDLE NAME:	
	RESIDENCE & CITIZENSHIP	CITY: Dourdan	STATE OR FOREIGN COUNTRY: France	COUNTRY OF CITIZENSHIP: British	
	POST OFFICE ADDRESS	POST OFFICE ADDRESS: 39 avenue de Paris	CITY: Dourdan	STATE OR COUNTRY: France	ZIP CODE: 91410
203	FULL NAME* OF INVENTOR	FAMILY NAME: MONTEL	GIVEN NAME: Jean	MIDDLE NAME:	
	RESIDENCE & CITIZENSHIP	CITY: Chatou	STATE OR FOREIGN COUNTRY: France	COUNTRY OF CITIZENSHIP: french	
	POST OFFICE ADDRESS	POST OFFICE ADDRESS: 3 rue Le Val Sablon	CITY: Chatou	STATE OR COUNTRY: France	ZIP CODE: 78400

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 201*	SIGNATURE OF INVENTOR 202*	SIGNATURE OF INVENTOR 203*
DATE 03 August 1998	DATE 03 August 1998	DATE 03 August 1998

☐ Additional inventors are named on separately numbered sheets attached hereto.